(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 788 350 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
27.02.2002 Bulletin 2002/09

(21) Application number: **95938091.6**

(22) Date of filing: **03.11.1995**

(51) Int Cl.[7]: **A61K 9/14**, A61K 9/50, B01J 13/02

(86) International application number:
PCT/SE95/01302

(87) International publication number:
WO 96/14833 (23.05.1996 Gazette 1996/23)

(54) SMALL PARTICLE FORMATION

HERSTELLUNG KLEINER PARTIKEL

FORMATION DE PETITES PARTICULES

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
LT LV

(30) Priority: **09.11.1994 SE 9403846**

(43) Date of publication of application:
13.08.1997 Bulletin 1997/33

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Description

[0001] The present invention is concerned with the formation of small particles of organic compounds upon precipitation when a solution of such an organic compound in a water-miscible solvent is added to an aqueous medium containing polymer and an amphiphilic compound (surfactant or lipid) at a concentration at which polymer/amphiphile complexes are formed. At said concentrations, the system is a solution below the critical concentration at which free micelles are formed. Upon addition of the organic compound, the compound interacts with the polymer/amphiphile complexes, thus increasing their hydrophobicity and leading to precipitation of organic compound/polymer/amphiphile aggregates.

[0002] According to the present invention, a small particle refers to a particle size of less than 2 μm.

[0003] The object of the invention is to provide a process for the formation of small particles of organic compounds, especially pharmaceutically active compounds, where such process does not involve emulsification or water-immisicible solvents.

[0004] The process is preferably used to prepare a readily soluble pharmaceutically active compound.

Background of the invention

[0005] From a pharmaceutical point of view, the smaller the particle size of a relatively insoluble drug, the grater is its rate of solution and as a rule, the greater is its bioavailability (J.H. Fincher, J. Pharm. Sci., 57, 1825 (1968)). To this end, small particles are conventionally formed by mechanical subdivision of bulk matter or by aggregation of small molecules or ions (D.J. Shaw, "Introduction to Colloid and Surface Chemistry", 3rd Ed., Butterworths, London, 1980, Chapter 1).

[0006] Studies of polymer/amphiphile systems in aqueous media have shown that interactions of polymers with charged amphiphiles occur in different stages. Ionic polymers and charged amphiphiles of opposite charge precipitate accordingly by electrostatic interactions. On the other hand, interactions between non-ionic polymers and amphiphiles occur in three stages. In the most dilute solutions, very little physical biding occurs. At concentrations of amphiphile higher than the critical micelle concentration, true micelles form. However, between these two concentrations, complexation or binding of polymer to amphiphile occurs (M.L. Fishman and F.R. Eirich, J. Phys. Chem., 75(20), 3135-40 (1971)). Small polymer/amphiphile aggregates or sub-micelles are thus formed. The presence of the amphiphile introduces an effective attraction between different polymer molecules since the formed aggregates could involve more than one polymer molecule. This attraction, together with the binding of the amphiphile to the polymer would lead to an increase in the hydrophobicity of the polymer. If the aggregate is sufficiently hydrophobic it will precipitate. The addition of a polar water-soluble compound (e.g. NaCl) to a polymer/amphiphile system will further enhance the precipitation of the polymer/amphiphile aggreates because there will be an increased difference in polarity between the solvent and the polymer/amphiphile aggregates and because the polar compound will tend to decrease the number of water molecules available for the hydration of the polymer/amphiphile aggregates. Also, precipitation occurs on increasing the temperature of systems containing polymers for which solubility is inversely related to temperature, such as cellulosic derivatives. The cloud point of hydroxypropylmethylcellulose (HPMC) has been shown to be lowered by addition of amphiphiles, the effect being more pronounced in the presence of salt (J.-E. Löfroth, L. Johansson, A.-C. Norman, and K. Wettström, Progr. Colloid. Polym. Sci., 84, 73-77 (1991)).

[0007] On the other hand, if a hydrophobic compound is added, it will tend to interact with the polymer/amphiphile aggregates, thus increasing the hydrophobicity of these polymer/amphiphile aggregates and facilitating their precipitation.

Summary of the invention

[0008] A method has now been found which surprisingly involves the formation of small particles, the growth of which is limited by the adsorption and/or concentration of polymer/amphiphile aggregates at the solid/liquid interface.

[0009] Thus, the invention concerns a process for preparing small particles comprising an organic compound, the solubility of which is greater in a water-miscible first solvent than in a second solvent which is aqueous, which process comprises the following steps:

(i) dissolving said organic compound in the water-miscible first solvent,

(ii) preparing a solution of a polymer and an amphiphile in the aqueous second solvent and in which second solvent the organic compound is substantially insoluble whereby a polymer/amphiphile complex is formed, and

(iii) mixing the solutions from steps (i) and (ii) so as to cause precipitation of an aggregate comprising the organic compound and the polymer/amphiphile complex.

[0010] The new method for the formation of small particles of an organic compound comprises:

1) Dissolving said compound in a first solvent which is water-miscible and in which said compound is soluble.

2) Preparing a solution of polymer and amphiphile

in a second solvent which is aqueous and in which the compound for which small particles are desired is more or less insoluble, preferably at concentrations below the critical concentration at which free micelles begin to form. The concentrations of polymer and amphiphile are such that they interact, but the critical micelle concentration of the amphiphile is not reached. The hydrophobicity of the polymer is thus increased to a desired degree at which no precipitation occurs. Precipitation of the polymer could also be prevented by temperature control in the cases where solubility of the polymer is a function of temperature.

3) Mixing the solutions from steps (1) and (2) while stirring. The organic compound interacts with the polymer/amphiphile complexes, thus increasing their hydrophobicity, and precipitation of drug/polymer/amphiphile aggregates occurs.

4) The formed particles are then separated, preferably by flocculation and collected by suitable means.

[0011] An organic compound for use in the process of this invention is any organic chemical entity whose solubility decreases from one solvent to another. This organic compound might be a pharmaceutically active compound from various groups such as, but not limited to: antihyperlipidemics, antimicrobials, e.g. sulfadiazine; non-steroidal antiinflammatories, e.g., indomethacin; antihypercholesteremic agents, e.g., probucol; and steroidal compounds, e.g., dexamethasone. Or the organic compound might be from the group used as adjuvants or excipients in pharmaceutical preparations and cosmetics, such as, but not limited to, preservatives, e.g., propylparaben.

[0012] The small particles obtainable by the process of the present invention comprising a pharmaceutically active compound and a pharmaceutical adjuvant may be used for the preparation of a pharmaceutical formulation.

[0013] The first solvent according to the present invention is a solvent or mixture of solvents in which the organic compound of interest is relatively soluble and which is miscible with the second solvent. Examples of such solvents include, but are not limited to: methanol, ethanol, isopropanol, acetone, dimethylformamide, and acetonitrile.

[0014] The second solvent according to the present invention is water or an aqueous solution containing one or more of various additives, such as, but not limited to:

1. polymers, such as dextrans; polyethylene glycols; polyvinylpyrrolidone; cellulosic derivatives, e.g., methylcellulose and hydroxypropylmethylcellulose; gelatin; and carrageenan.

2. salts, such as monovalent ions, e.g., sodium chloride; divalent ions, e.g., sodium sulfate and calcium chloride; and trivalent ions, e.g., aluminum chloride.

3. surfactants such as nonionics, e.g., sorbitan fatty acid esters and their polyoxyethylene derivatives; anionics, e.g., sodium dodecylsulfate; and cationics, e.g., cetyltrimethylammonium bromide.

4. viscosity enhancing agents, such as, hydrophilic colloids, e.g., gelatin, acacia and tragacanth.

5. cosolvents, such as glycerol, propylene glycol, methanol, ethanol and isopropanol.

[0015] A polymer according to the invention, the solution of which is prepared in the second solvent, is meant to be a wide variety of organic chemical entities of relatively high molecular weight, such as, but not limited to:

1. vinyl derivatives, e.g., polyvinylpyrrolidone.

2. cellulose derivatives, e.g., methylcellulose and hydroxypropylmethylcellulose.

3. polyethylene glycols, e.g., polyethylene glycol 6,000 and polyethylene glycol 10,000.

4. a pharmaceutically acceptable adjuvant.

[0016] An amphiphile according to the invention is a compound, the molecules of which consist of two parts, one of which is hydrophilic and the other of which is hydrophobic in nature. These compounds include, but are not limited to:

1. nonionics, e.g., cholesterol, lecithin, sorbitan fatty acid esters and their polyoxyethylene derivatives.

2. anionics, such as, alkylsulfates, e.g., sodium dodecylsulfate; and bile salts, e.g., sodium cholate and sodium taurocholate.

3. cationics, e.g., cetyltrimethylammonium bromide and benzalkonium chloride.

[0017] The concentration of the organic compound in the first solvent can be as low as 0.01% by weight and as high as, but not limited to, the saturation concentration of the organic compound in the first solvent, including concentrations which form supersaturated solutions within the range of temperatures up to the boiling point of the first solvent.

[0018] The concentration of the polymer can be ranging from 0.01% to 50% by weight in the second solvent, preferably 0.01% to 10%.

[0019] The concentration of the amphiphile can be ranging from 0.001% to 50% by weight in the second solvent, preferably 0.001% to 5%.

[0020] Flocculation can be achieved by various modes, such as

1. addition of an electrolyte, such as, but not limited to, sodium sulfate, sodium phosphate and potassium phosphate.

2. temperature change.

3. addition of a high molecular weight polymer (bridging flocculation).

[0021] Collection of the small particles can be achieved by various methods, such as, but not limited to:

1. centrifugation and ultracentrifugation.

2. filtration.

3. reverse osmosis followed by evaporation.

4. evaporation of the solvent by heating and/or vacuum.

5. freeze-drying.

6. spray-drying.

7. fluidized-bed drying.

8. any combination of the above.

Detailed description of the Invention

[0022] According to one embodiment of the invention, the process comprises the following steps:

1) Dissolving a pharmaceutically active compound, such as an antihyperlipidemic agent, in a first solvent which is water-miscible;

2) Dissolving polyvinylpyrrolidone and sodium dodecylsulfate in a second solvent which is aqueous such as water and in which the active compound is more or less insoluble. The concentrations of both polyvinylpyrrolidone and sodium dodecylsulfate are such that the system is below the critical concentration at which free micelles form and precipitation of the polymer/amphiphile complex has not occurred.

3) Adding the solution obtained from step (1) to that prepared in step (2) while keeping the latter under constant agitation. Precipitation occurs and results in a suspension of drug/polymer/amphiphile small particles.

4) The small particles thus obtained are flocculated by the addition of an aqueous solution of an electrolyte, such as potassium phosphate.

5) The suspension is centrifuged and washed twice with water, centrifuged (so as to preferably obtain aggregates of less than 2 μm in size), redispersed in water and then freeze-dried.

[0023] The process of forming small particles according to the invention is illustrated by the following example:

EXAMPLE

[0024] A solution consisting of 1 g of probucol (a lipid lowering drug) and 12 ml of absolute ethanol was added to a solution consisting of 2 g polyvinylpyrrolidone (M. W. 360.000), 0.1 g sodium dodecylsulfate and 50 ml water while stirring at 1.200 rpm with a magnetic stirrer. This procedure resulted in a white suspension of small particles comprising probucol. The small particles were then flocculated by adding a potassium phosphate solution. The flocculated small particles were separated by centrifugation, washed twice with water, redispersed by sonication and then freeze-dried. The process was monitored by observation of samples in the optical microscope. The final freeze-dried product was observed by electron microscopy; agglomerates of small particles of less than 2 μm were observed.

Claims

1. A process for preparing small particles comprising an organic compound, the solubility of which is greater in a water-miscible first solvent than in a second solvent which is aqueous, which process comprises the following steps:

   (i) dissolving said organic compound in the water-miscible first solvent,

   (ii) preparing a solution of polymer and an amphiphile in the aqueous second solvent and in which second solvent the organic compound is substantially insoluble whereby a polymer/amphiphile complex is formed, and

   (iii) mixing the solutions from steps (i) and (ii) so as to cause precipitation of an aggregate comprising the organic compound and the polymer/amphiphile complex.

2. A process according to claim 1, wherein the polymer and amphiphile present in the solution produced according to step (ii) are at concentrations below the critical concentration at which free mi-

celles begin to form.

3. A process according to claim 1 wherein flocculation of the precipitated aggregate is achieved by the addition of an electrolyte, and thereafter separation of the aggregate is achieved by means of centrifugation so that aggregates of less than 2μm in size are separated out.

4. A process according to any one of the preceding claims wherein the polymer and the amphiphile are mixed in solution, interact and are precipitated by the addition of a hydrophobic organic compound.

5. A process according to any one of the preceding claims wherein the compound is pharmaceutically active.

6. A process as claimed in claim 5 wherein the pharmaceutically active compound is an antihyperlipidemic agent.

7. A process according to any one of the preceding claims in which the polymer is a pharmaceutically acceptable adjuvant.

8. The use of small particles comprising a pharmaceutically active compound and a pharmaceutical adjuvant when produced by a process as claimed in any one of claims 1 to 7 in the preparation of a pharmaceutical formulation.

Patentansprüche

1. Verfahren zur Herstellung kleiner Teilchen, die eine organische Verbindung enthalten, deren Löslichkeit in einem mit Wasser mischbaren ersten Lösungsmittel größer ist als in einem wäßrigen zweiten Lösungsmittel, wobei das Verfahren die folgenden Schritte umfaßt:

   (i) Lösen der organischen Verbindung in dem mit Wasser mischbaren ersten Lösungsmittel,
   (ii) Darstellung einer Lösung von einem Polymer und einer amphiphilen Verbindung in dem wäßrigen zweiten Lösungsmittel, in dem die organische Verbindung im wesentlichen unlöslich ist, wobei ein Komplex aus Polymer und amphiphiler Verbindung gebildet wird, und
   (iii) Vermischen der Lösungen aus Schritt (i) und (ii) derart, daß ein Aggregat ausfällt, das die organische Verbindung und den Komplex aus Polymer und amphiphiler Verbindung umfaßt.

2. Verfahren nach Anspruch 1, wobei das Polymer und die amphiphile Verbindung, die in der nach Schritt (ii) dargestellten Lösung vorhanden sind, in Konzentrationen vorliegen, die unterhalb der kritischen Konzentration liegen, bei der die Bildung von freien Mizellen einsetzt.

3. Verfahren nach Anspruch 1, bei dem man durch Zugabe eines Elektrolyts eine Ausflockung des ausgefallenen Aggregats erzielt und anschließend das Aggregat durch Zentrifugation dermaßen abtrennt, daß Aggregate einer Größe von weniger als 2 μm abgetrennt werden.

4. Verfahren nach einem der vorhergehenden Ansprüche, wobei das Polymer und die amphiphile Verbindung in Lösung vermischt werden, miteinander wechselwirken und durch Zugabe einer hydrophoben organischen Verbindung ausgefällt werden.

5. Verfahren nach einem der vorhergehenden Ansprüche, bei dem die Verbindung pharmazeutisch wirksam ist.

6. Verfahren nach Anspruch 5, wobei es sich bei der pharmazeutisch wirksamen Verbindung um ein antihyperlipidämisches Mittel handelt.

7. Verfahren nach einem der vorhergehenden Ansprüche, bei dem es sich bei dem Polymer um ein pharmazeutisch unbedenkliches Adjuvans handelt.

8. Verwendung von kleinen Teilchen, enthaltend eine pharmazeutisch wirksame Verbindung und ein pharmazeutisches Adjuvans bei Darstellung durch ein Verfahren nach einem der Ansprüche 1 bis 7, zur Herstellung einer pharmazeutischen Formulierung.

Revendications

1. Procédé de préparation de petites particules comprenant un composé organique, dont la solubilité dans un premier solvant miscible à l'eau est plus élevée que dans un deuxième solvant qui est aqueux, lequel procédé comprend les étapes suivantes :

   (i) on dissout ledit composé organique dans le premier solvant miscible à l'eau,
   (ii) on prépare une solution de polymère et d'un agent amphiphile dans le deuxième solvant aqueux et dans lequel deuxième solvant le composé organique est sensiblement insoluble, de sorte qu'un complexe polymère/agent amphiphile est formé, et
   (iii) on mélange les solutions des étapes (i) et (ii) de manière à provoquer la précipitation d'un agrégat comprenant le composé organique et

le complexe polymère/agent amphiphile.

2. Procédé selon la revendication 1, **caractérisé en ce que** le polymère et le agent amphiphile présent dans la solution produite selon l'étape (ii) sont à des concentrations inférieures à la concentration critique à laquelle des micelles libres commencent à se former.

3. Procédé selon la revendication 1, **caractérisé en ce que** la floculation de l'agrégat précipité est assurée par l'addition d'un électrolyte, et ensuite la séparation de l'agrégat est assurée par centrifugation pour que les agrégats de taille inférieure à 2 µm soient séparés.

4. Procédé selon l'une quelconque des revendications précédentes, **caractérisé en ce que** le polymère et le agent amphiphile sont mélangés en solution, interagissent et sont précipités par l'addition d'un composé organique hydrophobe.

5. Procédé selon l'une quelconque des revendications précédentes, **caractérisé en ce que** le composé est pharmaceutiquement actif.

6. Procédé selon la revendication 5, **caractérisé en ce que** le composé pharmaceutiquement actif est un agent anti-hyperlipidémiant.

7. Procédé selon l'une quelconque des revendications précédentes, dans lequel le polymère est un adjuvant pharmaceutiquement acceptable.

8. Utilisation de petites particules comprenant un composé pharmaceutiquement actif et un adjuvant pharmaceutique lorsqu'elles sont produites par un procédé selon l'une quelconque des revendications 1 à 7, dans la préparation d'une formulation pharmaceutique.